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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/720,037	RASPE ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *4-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

Applicants' response of 11 December 2008 is acknowledged. Claims 1-3, and 9-13 have been amended and the amendment made of record. New claims 14 and 15 have been presented and made of record.

Claims 1-15 are pending in the instant invention. Claims 4-8 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

It is noted that claims 3 and 9 have been amended to recite "providing a nuclear factor which is capable of functionally coupling said hRev-erb to an RNA-polymerase complex and measuring the binding [of test substance] to a nuclear factor capable of functionally coupling said hRev-erb to the RNA-polymerase complex."

In Requirement for Restriction of 18 June 2008, the Examiner grouped the claims 1-3 and 9-13 of the instant invention into three inventive groups:

Group I, claim(s) 1-3, and 9-13, as drawn to a method of screening for a substance useful in the treatment of a lipid metabolism dysfunction comprising contacting said substance with a Rev-erb receptor.

Group II, claim(s) 1-3, and 9-13, as drawn to a method of screening for a substance useful in the treatment of a lipid metabolism dysfunction comprising contacting said substance with a Rev-erb response element.

Group III, claim(s) 3, and 9-13, as drawn to a method of screening for a substance useful in the treatment of a lipid metabolism dysfunction comprising contacting said substance with a nuclear factor capable of functionally coupling Rev-erb to the RNA polymerase complex.

In response of 26 June 2008, Applicants elected Group I, claims 1-3 and 9-13, drawn to a method of screening for a substance useful in the treatment of a lipid metabolism dysfunction comprising **contacting said substance with a Rev-erb receptor**.

Newly submitted amendment to claims 3 and 9 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: as noted above, the claims recite "providing a nuclear factor which is capable of functionally coupling said hRev-erb to an RNA-polymerase complex and measuring the binding [of test substance] to a nuclear factor capable of functionally coupling said hRev-erb to the RNA-polymerase complex." These limitations were recited in Group III.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits.

Therefore, the claims will be examined to the extent they read on the elected invention:

A method of screening for a substance which is useful in the treatment of a lipid metabolism dysfunction comprising contacting said substance with a human Rev-erb receptor or a protein which at least comprises the hRev-erb ligand binding domain and the hRev-erb DNA binding site (independent claim 1), providing a hRev-erb response element or a polynucleotide sequence onto which said Rev-erb receptor is capable of binding thereto; and detecting the transcriptional activity, of a gene which is under the control of a promoter comprising said response element in the presence and absence of said test substance (Claim 1).

A process for screening a substance which is useful in the treatment of a lipid metabolism dysfunction comprising placing a test substance in contact with a receptor of the Rev-erb family (hRev-erb) or a protein which at least comprises the hRev-erb ligand binding site and the hRev-erb DNA binding site, providing a human Rev-erb receptor response element or a polynucleotide sequence onto which said hRev-erb is capable of binding thereto, and measuring the binding of said test substance to the Rev-erb receptor or the binding of the a test substance-hRev-erb receptor complex to said hRev-erb response element and optionally detecting the modulation of the transcriptional activity of a gene which is under the control of a promoter comprising the hRev-erb response element (Claim 3).

A method for characterization or testing of the mechanism of action of a substance having anti-atherosclerotic properties comprising placing said substance in contact with a receptor of the Rev-erb family (hRev-erb) or a protein which at least comprises the hRev-erb ligand binding site and the hRev-erb DNA binding sites, providing a human Rev-erb receptor response element or a polynucleotide sequence onto which said hRev-erb capable of binding thereto, and measuring the binding of said substance to the Rev-erb receptor or the binding of the test substance-hRev-erb receptor complex to said hRev-erb response element and optionally detecting the modulation of the transcriptional activity of the a gene which is under the control of a promoter comprising the hRev-erb response element (Claim 9).

Information Disclosure Statement:

The information disclosure statement filed 11 December 2008 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because Reference 1 could not be found among the papers submitted on the 11 December 2008. It has been crossed out and the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Withdrawn Rejections

The rejection of Claims 1, 3, and 9 under 35 U.S.C. 112, second paragraph, as being incomplete method claims is withdrawn in light of Applicants' amendment to the claims.

The rejection of Claims 1, 3, and 9 under 35 U.S.C. 112, second paragraph as vague and indefinite in reciting "functional equivalent thereof" is withdrawn in light of Applicants' amendment to the claims.

The rejection of Claims 10 and 12 under 35 U.S.C. 112, second paragraph is withdrawn in light of Applicants' amendment to the claims.

The rejection of Claims 1-3 and 9-13 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in light of Applicants' amendment to the claims.

The rejection of Claims 1-3, and 9 under 35 U.S.C. 102(e) as being anticipated by Trueheart et al. (US 6,189,705, issued 12 December 2000, filed 24 September 1997, the '705 patent) is withdrawn in light of Applicants' amendment to the claims.

The rejection of Claims 10-13 under 35 U.S.C. 103(a) as being unpatentable over the '705 patent as applied to claims 3 and 9 in view of Vu-Dac et al (1998. J Biol Chem. 273:25713-25720, page 25717) and further, in view of Fraser et al. (1997. J. Biol Chem. 1997. J Biol Chem. 272:13892-13898) and Auwerx et al. (1996. Atherosclerosis 124 Suppl:S29-S37) is withdrawn in light of Applicants' amendment to the claims.

Maintained/New Grounds of Objections/Rejections

Objections

Specification:

The objection to the specification because it does not contain a brief description of the drawings is maintained. Applicants' have failed to address this objection in response of 11 December 2008.

It is noted that applicants have listed references at the conclusion of the specification (pages 31-40). The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be

submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Sequence Rules:

The specification is not in compliance with the requirements of 37 CFR 1.821 through 1.825 of the Sequence Rules and Regulations. Specifically the application fails to comply with CFR 1.821(d), which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequences by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text or claims of the patent application.

37 CFR 1.821(a) presents a definition for nucleotide and/or amino acid sequences. This definition sets forth limits in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amno acids or an unbranched sequence of ten or more nucleotides. Please see MPEP 2422.01

The specification discloses polynucleotide sequences on page 3, line 11, and Table 1. However, these sequences are not identified by sequence identifiers nor have they been listed in a sequence listing.

For compliance with sequence rules, it is necessary to include the sequences in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.82(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03). **Compliance with the sequence rules is required**.

Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action

Claims:

Claims 3 and 9 are objected to as reciting non-elected inventions. The claims should be amended to recite only the elected invention.

Claim 11 is objected to because of the following informalities: there is an omission of the preposition "of" in between the words "activity" and "said" in line 2 of the claim. Appropriate correction is required.

Rejections

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9, 12, and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of Claim 9 as vague and indefinite in reciting "A method for characterization or testing of the mechanism of action of a substance having anti-atherosclerotic properties comprising placing said substance in contact with the receptor of the Rev-erb family ….and measuring the binding of said substance to the Rev-erb receptor" is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Response of 11 December 2008, page 7, 1st paragraph). The reason for the traversal is:

Applicants disagree that the preamble of the claim is directed to testing of a mechanism of action, as alleged by the Office Action. The present claims are directed to *a method of screening for a test substance*.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

As previously stated the method steps recited in claim 9 are directed to a binding assay and are essentially identical to method steps recited in claim 3. To distinguish the claim 9 from claim 3 one must consider the recitation of intent in the preamble.

The courts have held that "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999). See also *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003) (See MPEP 211.02). The intended use, "a method for characterization or testing of a mechanism of action of a substance having anti-atherosclerotic properties' is all that distinguishes claim 9 from claim 3. Therefore, applicants must recite steps to accomplish the stated goal.

Claims 12 and 13 are included in the rejection as dependent upon a rejected claim.

35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trueheart et al. (US 6,189,705, issued 12 December 2000, filed 24 September 1997, the '705 patent) in view of Harding et al (1995, Mol and Cell Biol 15:4791-4802) further in view of Vu-Dac et al (1998. J Biol Chem. 273:25713-25720,

The cited references establish the following fact pattern:

The '705 patent teaches general methods for screening and identifying pharmaceutically effective compounds that specifically interact with and modulate activity of a cellular receptor (abstract). The subject assays provide a means for detecting the ability of compounds to modulate the signal transduction activity of the target receptor by scoring for up or down regulation-regulation of a detection signal (column 2, lines 46-49). Signal transduction may be measured using a reporter gene to provide a convenient readout (column 2, lines 54-55). The compounds to be screened are exogenously added to cells comprising a heterologous receptor (column 3, lines 53-55) in order to identify potential effector compounds (column 3, lines 13-15). The heterologous receptors may be mammalian, for example, human (column 8, lines 64-65). Among receptors to be used to screen for cognate ligands are nuclear receptors including orphan receptors such as Rev-erb (column 22, line 57). Thus, the '705 patent teaches that the referenced methods may be used to screen for test compounds that bind to nuclear receptors such as the human rev-erb receptor. The assay uses a test cell which includes a target receptor (e.g. the rev-erb receptor) whose signal transduction activity can be modulated by interaction with an extracellular signal (test compound), the transduction activity being able to generate a detectable signal. The cell also includes a detection means, such as a reporter gene or an indicator gene, for

detecting signals produced by the receptor (column 13, lines 19-31). The reporter gene construct is a nucleic acid that includes a reporter gene operatively linked to at least one transcriptional regulatory sequence (response element). Transcription of the reporter gene is controlled by the regulatory sequence (promoter sequence) (column 12. lines 36-54). Thus, the '705 patent teaches an assay to screen test compounds. Said assay comprises the following components: a test compound (test substance), a heterologous receptor which may be the human Rev-erb receptor, and a reporter construct comprising a promoter region whose expression is modulated by the target receptor (response element onto which said Rev-erb receptor is capable of binding). The ability of compounds to modulate the signal transduction activity of the target receptor by is assessed by scoring for up or down regulation-regulation of a detection signal. The '705 patent does not teach a method comprising providing an hRev-erb response element onto which said Rev-erb receptor is capable of binding thereto, nor does it teach identification of a test substance that is useful in the treatment of lipid metabolism dysfunction.

Harding et al teaches that human Rev-Erb binds as a monomer to the thyroid/retinoic acid receptor half-site AGGTCA flanked 5' by an A/T-rich sequence (Rev monomer site) (abstract); in addition, the the Rev-Erb receptor binds as a homodimer to repress transcription of gene containing a Rev-DR2 response element. Thus, the reference teaches several possible Rev-erb response elements onto which the Rev-erb receptor is capable of binding thereto.

Vu-Dac et al teach that fibrates, which are hypolipidemic drugs, elevate mRNA levels of the nuclear receptor Rev-erbα. The resulting increase in Rev-erbα protein represses the transcription of Apolipoprotein A-1 (Apo-1) gene, thereby lowering cholesterol (abstract), thus teaching a substance that is useful in the treatment of a lipid metabolism dysfunction acting through Rev-erbα and establishing a nexus between Rev- erbα protein and the amelioration or treatment of lipid metabolism dysfunction.

Thus, aware of the teachings of the above references, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to

modify the teachings of the '705 patent, modifying the screening assay taught by the '705 assay and substitute one of the response elements taught by Harding et al which bind the human Rev-erb receptor for the generic regulatory sequence (promoter sequence) taught by the '705 method and use the modified assay to screen for test compounds useful in treatment of a lipid metabolism dysfunction. The person of ordinary skill in the art would have been motivated to make these modifications and anticipate success because the '705 patents teach an assay method useful for screening and identifying pharmaceutically effective compounds that specifically interact with and modulate activity of a cellular receptor, the Rev-Erb receptor, Harding et al identify specific response elements which bind the Rev-Erb receptor and act to repress transcription of gene operationally linked to said receptor and Vu-Dac teach that Rev-erbα protein activity represses the transcription of Apolipoprotein A-1 (Apo-A1) gene, thereby lowering cholesterol.

Applicants traverse the rejection of claims 1-3, and 9 under 35 U.S.C. 102(e) as being anticipated by the '705 patent in the previous Office Action (Response of 11 December 2008, page 9). The reasons for the traversal are:

1. there is no mention of human Rev-erb of the present invention.

2. the '705 patent teaches assay techniques which utilize hormone-dependent reporter constructs such as GRE response elements and thyroid receptor enhancer-like DNA sequences. The reference is silent with respect to human Rev-erb response elements.

3. the '705 patent is silent with respect to hRev-erb polypeptides and response elements thereof.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to Applicants' amendment to the claims, claims 1, 3 and 9 are now rejected under 35 U.S.C. 103(a), not under 35 U.S.C. 102(e).

In response to 1: the '705 patent teaches utilization of Rev-erb receptors in the method of the instant invention (column 22, line 57); such receptors may be of human origin (column 8, lines 64-65).

In response to 2 and 3: The '705 patent teaches the use of hormone-dependent reporter constructs as a preferred embodiment, but not as the only embodiment. The reference teaches the use of reporter gene constructs that include reporter genes operatively linked to at least one transcriptional regulatory sequence (response element) (column 12. lines 36-54). The response element is not further identified. One of ordinary skill in the art would recognize the utility of constructing a reporter gene construct comprising a response element that binds its cognate nuclear receptor, that is a response element that binds the Rev-erb receptor. These response elements are taught by the Harper reference

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over the '705 patent in view of Harding et al and Vu-Dac et al as applied to claim 1, further in view of Adelmant et al (1996. PNAS 93:3553-3558).

The teachings of the '705 patent, Harding et al and Vu-Dac et al are outlined in detail above. These references, singularly or in combination, do not teach a method of screening for a substance wherein the Rev-erb receptor is specifically the hRev-erbα receptor and the Rev-erb receptor response element is specifically the hRev-erbα response element.

Adelmant et al. teach the rev-erb gene encode two highly related orphan receptors named Rev-erbα and Rev-erbβ and teach a hRev-erbα responsive element (page 3553, 1st column 2nd paragraph).

Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '705 patent, Harding et al and Vu-Dac et al and substitute the human Rev-erb**α** receptor and human Rev-erb**α** response element as taught by Adelmant et al. for the generic Rev-erb receptor and the generic Rev-erb receptor response elements taught by the '705 patent and Harding et al. The person of ordinary skill in the art would have been motivated to make these modifications and anticipate success because one of ordinary skill in the art would recognize the advantage of substituting a specific human Rev-erb**α** receptor and human Rev-erb**α** response element for the generic ones disclosed by the '705 patent and the

Harding reference and would recognize the utility of screening for compounds that would be potential therapeutic agents for treatment of human lipid metabolism dysfunction, e.g. for the treatment of hypercholesterolemia or elevated triglycerides

Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over the '705 patent in view of Harding et al and Vu-Dac et al as applied to claims 3 and 9 further, in view of Fraser et al. (1997. J. Biol Chem.272:13892-13898) and Auwerx et al. (1996. Atherosclerosis 124 Suppl:S29-S37). The teachings of the '705 patent, Harding et al and Vu-Dac et al are set forth in detail above. Additionally, the '705 patent teaches that identified test compounds identified by the described assay can be formulated in pharmaceutical preparations for in vivo administration to a human (column 56, lines 35'43). The three references, singularly or in combination, do not teach a method wherein the gene is the apolipoprotein C-III (apo C-III) (Claim 10 and 12), wherein a reduction of transcriptional activity of said apo C-III in the presence of said test compound indicates that said test compound is useful in the treatment of a lipid metabolism dysfunction (claim 11) or wherein a reduction of transcriptional activity of said apoC-III in the presence of said test compound indicates that said test compound has anti-atherosclerotic property (Claim 14).

As indicated above, Vu-Dac et al teach that rev-erbα inhibits the transcription of Apolipoprotein A-1 (Apo-A1). In addition, the reference teaches that fibrates, which are hypolipidemic drugs, elevate mRNA levels of the nuclear receptor Rev-erbα and have been shown to repress the transcription of a wide variety of genes involved in lipid and energy metabolism including the human, rat and mouse ApoC-III genes (page 29718, 2nd column, 2nd paragraph). Fraser et al. teach that Apo-AI and apo-CIII genes are closely linked and appear to share regulatory elements (page 13892, 2nd column, 2nd paragraph), leading one of ordinary skill in the art to conclude that the nuclear receptor Rev-erbα DNA binding domain would bind to the regulatory element (response element) for Apo-CIII also. Auwerx et al teach that decreases in Apo CIII protein concentration induces beneficial changes in lipoprotein profile and further teach that altering the

expression of genes encoding for apolipoproteins constitutes an effective therapeutic option (page S35, section 5).

Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made, aware of the teachings of Fraser et al and Auwerx et al, to modify the teachings of the '705 patent, Harding et al and Vu-Dac and measure changes in the transcriptional activity of ApoC-III gene as a specific measure of signal transduction following binding of test compound to the rev-erbα receptor and identifying an agent that decreases the transcriptional activity of Apo-CIII as a compound useful in treatment of a lipid metabolism dysfunction and having anti-atherosclerotic property. The person of ordinary skill in the art would have been motivated to make these modifications and anticipate success because Vu-Dac et al. teach that Rev-erbα protein represses the transcription of Apolipoprotein A-1 (Apo-A1) gene, Fraser et al. teach that Apo-1 and Apo-CIII genes appear to share regulatory elements and may thus be regulated by the same receptor protein, such as the rev-erbα receptor, Auwerx et al teaches the therapeutic benefits of decreasing expression of genes encoding the Apo-CIII protein and the '705 patent teaches that test compounds identified by the screening assays taught in the reference are useful as therapeutic compounds.

Applicants traverse the rejection of claims 10-13 under 35 U.S.C. 103(a) in the previous Office Action (Response of 11 December 2008, page 10). The reasons for the traversal are:

1. vu-Dac is silent with regard to the effect of Rev-erb receptor on Apo C-III expression levels

2. There is no mention that the interaction of hRev-erb with its cognate response element results in negative regulation of Apo C-III.

3. The '705 patent expressly teaches that the methods are applicable for screening of compounds which change the activity of GPCRs or EPH receptors.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

In response to 3: While the '705 patent teaches exemplary embodiments comprising assays to screen for compounds that bind to GPCRs or EPH receptors, the

teachings of the reference are not limited to these embodiments. As discussed above, the '705 patent also teachings utilization of the disclosed assay to screen for compounds that change the activity of nuclear receptors, including rev-erb receptors.

In response to 1and 2: While vu-Dac et al does not expressly teach that rev-erb receptors negatively regulates ApoC-III transcriptional activity, resulting in a decrease in expression of ApoC-III, the reference teaches that fibrates, which stimulate Rev-erb expression, repress the transcription of a number of genes involved in lipid and energy metabolism including human ApoC-III (page 25718, 2nd column, 2nd paragraph), thereby suggesting the possibility of negative regulation of ApoC-III by rev-erb receptor.

Claims 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over the '705 patent, in view of Harding et al and Vu-Dac et al as applied to claim 1 further, in view of Terenzi et al. (1996. Prot Express. and Purif. 8:313-318)

The teachings of the '705 patent, Harding et al and Vu-Dac et al are set forth in detail above. The three references, singularly or in combination, do not teach a method wherein hRev-erb receptor protein is a chimeric protein comprising said hRev-erb receptor protein and glutathione-S-transferase.

Terenzi et al teach a fusion protein comprising the DNA binding domain of a member of the Rev-erb family, Rev-erbβ and glutathione S-transferase (GST) (page 314, 2nd column, last two paragraphs). Additionally, the reference teaches that the receptor has a modular structure which can be divided into distinct domains and identifies the ligand binding domain (Figure 1). The reference teaches the advantages of the chimeric protein comprising GST in a purification protocol comprising use of glutathione-Sepharose.

Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of the '705 patent, Harding et al and Vu-Dac and use a chimeric protein comprising the Rev-erb receptor and GST in the assays taught by the '705 patent, Harding et al and Vu-Dac references. The person of ordinary skill in the art would have been motivated to make these modifications and anticipate success because Terenzi et al. teach the modular structure of Rev-erb and

teach the advantage of a protein comprising one of the modules (the DNA binding domain) and GST in purification of said protein. In addition, the modular construction of nuclear receptors is well known in the art, and making fusion proteins comprising said modules is routine in the art.

Conclusion:

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. H. S./
Examiner, Art Unit 1647

/Manjunath N. Rao, /
Supervisory Patent Examiner, Art Unit 1647